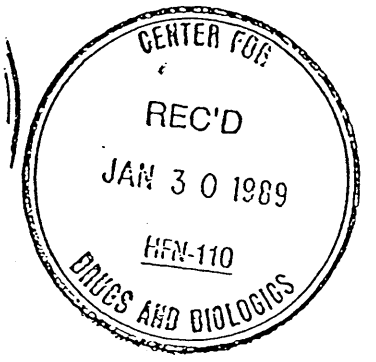
DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION

MINUTES



CARDIOVASCULAR AND RENAL DRUGS ADVISORY COMMITTEE

Fifty-Ninth Meeting

Thursday, October 5, 1989
Friday, October 6, 1989

Jack Masur Auditorium
Building 10
National Institutes of Health
9000 Rockville Pike
Bethesda, Maryland

P A R T I C I P A N T S

Committee:

Craig M. Pratt, M.D. Chairman

Carl V. Leier, M.D.
David T. Lowenthal, M.D., Ph.D.
Franz H. Messerli, M.D.
Milton Packer, M.D.
Jeremy Ruskin, M.D.
D. Craig Brater, M.D.
Frank E. Harrell, Jr., Ph.D.
Edward L.C. Pritchett, M.D.

Invited Guests:

Philip J. Podrid, M.D.
Albert M. Waldo, M.D.
Doulgas P. Zipes, M.D.
Peter J. Schwartz, M.D.

Consultants:

Peter R. Kowey, M.D.

FDA Staff:

Robert J. Temple, M.D.
Raymond J. Lipicky, M.D.
Paula Botstein, M.D.
Stephen Fredd, M.D.
Joan C. Standaert, Executive Secretary

CAST:

Curt Furberg, M.D. - Bowman Grey
Larry Friedman, M.D., NHLBI
Alfred Hallstrom, Ph.D. - Director CAST Center
Salim Yusuf, M.D., D.Phil., NHLBI
Leon Greene, M.D. - CAST Cardiologist
Peter J. Schwartz, M.D. - Fielologia Clinica, Milan, Italy

3M - Riker:

Richard R. Wilson - 3M Riker
Michael T. Cullen, Jr., M.D. - 3M Riker
Jeffrey L. Anderson, M.D. - University of Utah School of Medicine
Rodolphe Ruffy, M.D. - University of Utah School of Medicine
Albert L. Waldo., M.D. - Case Western Reserve University

Aspirin PHS:

Charles Hennekens, M.D.
Julie Buring, Ph.D.
Samuel Goldhaber, M.D.
Bernard Rosner, Ph.D.
James Taylor, M.D.

This concluded the discussion of flecainide and the committee, after a brief recess, considered a possible modification for professional aspirin labeling which would introduce a new claim for the prevention of primary MI. This claim would be based on the results of the U.S. Physicians Health Study (PHS), presented by Dr. Charles Hennekens of Brigham and Young Hospital. These results were published in the N Engl J Med 1989:321:129-35.

This study was designed to test two primary hypotheses; did 325 mg of aspirin every other day reduce total cardiovascular mortality and did 50 mg of beta-carotene every other day decrease the incidence of cancer. 22,071 male physicians were enrolled, 11,037 were randomized to aspirin and 11,000 to aspirin placebo. This study was planned for an undetermined number of years.

In December of 1987 the Data Monitoring Board recommended early termination of the aspirin component of the trial, because of significant reduction of MI in the aspirin group and because the trial would be unable to detect the effect of aspirin on cardiovascular mortality. When final results of the aspirin phase were published in 1988 the mean duration of the study was 60 months.

The findings reported 139 total MI in the aspirin group vs 239 in placebo, a 44% reduction in incidence. The most significant reduction occurred in people over the age of 50. When all vascular endpoints non-fatal MI, non-fatal stroke and cardiovascular death were combined there was an 18%

reduction among the aspirin group, 307 deaths vs 370 deaths in placebo.

There were more strokes reported for the aspirin group than for placebo, 119 events vs 98 and there were 23 hemorrhagic strokes in the aspirin group vs 12 in placebo. Sudden death also favored placebo with 22 for aspirin and 12 in placebo. The major side effects were gastrointestinal, despite the fact that an 18 week run in period eliminated most patients intolerant to the medication.

Another trial in the primary prevention of cardiovascular disease was conducted in Britain on 5139 male doctors aged 50-75. This trial which used 500 mg aspirin daily showed no differences for MI, stroke or mortality between aspirin and the control group, which was asked to avoid aspirin.

FDA reviewers had some problems with the results of the PHS as presented. Dr. Hung, FDA Mathematical Statistician and Dr. Harrell Committee Biostatistician pointed out that because of the early stopping, significant adjustments in the analyses were required.

The FDA medical officer Dr. Triantas, undertook a review of records from the trial. Her review uncovered some patients who had evidence of a previous MI or other cardiovascular event. The implication of this finding was that in fact the aspirin group received some benefit from secondary prevention which was not available to the placebo group.

Other questions were raised by committee members relating to the patient population including concomitant use of cardiovascular medication, possible presence of atherosclerosis, coronary artery disease and silent MI. These variables could significantly influence the outcome of the trial.

The committee then addressed the questions developed by the FDA. A copy of the questions is appended to these minutes. Dr. Brater, committee reviewer, concluded that despite the early termination of the trial for reasons not previously specified in the protocol, the reduction of MI retained significance. The findings of undetected MI, PTCAs and CABGs did not alter the outcome.

The committee did not have confidence in efficacy for prevention of fatal MI alone, although combined fatal and non-fatal MI appeared to be reduced. Aspirin had no effect on total cardiovascular mortality. The numbers for fatal strokes were too small to reach a conclusion. The committee was divided 4-no, 3-yes that there was a significant effect for increased hemorrhagic stroke in the aspirin group.. The committee was also divided on the weight of the British Trial. They voted 4-no, 3- yes that this outcome influenced their evaluation of the PHS.

The committee voted 6-yes, 2-no (1 in absentia), that some type of primary claim for some group of patients could be developed. The committee was concerned that aspirin would be used in healthy people or inappropriate patient populations and would in addition be advertised for such use.

They voted unanimously that a claim for primary prevention should be separate from the existing claim for secondary prevention. The labeling should not

explicitly restrict use in hypertensive patients but should recommend that aspirin should only be used for primary prevention in high risk patients with risk factors. By a vote of 4-no, 2-yes they recommended separate dosing regimens for primary and secondary indications. They also recommended that regular package labeling, aside from professional labeling, carry a precaution like, "for other claims see your doctor". The committee then adjourned at 5:30 p.m..

I certify that I attended the October 5,6, 1989 meeting of the Cardiovascular and Renal Drugs Advisory Committee and these minutes accurately reflect what transpired.

Craig M. Pratt M.D.,
Chairman

Joan C. Standaert M.S.
Executive Secretary

QUESTIONS

Cardiovascular and Renal Drugs Advisory Committee

October 6, 1989

ASPIRIN

Aspirin is an Over-the-Counter drug and labeling for its Over-the-Counter use appears on the containers sold in stores. In addition, aspirin has indications (such as decreasing the risk of having a second myocardial infarction) which appear in Professional Labeling, but not on the containers sold. Professional Labeling has the same meaning as a package insert for a prescription only drug. It contains trial information, detailed indications, advice on how to use, and side effects. It is also the basis for regulation of drug promotion.

The U.S. Physician's Health Study (PHS) randomized about 22,000 male physicians, age 40-80 with no prior history of AMI to aspirin 325 mg q2d or to placebo to determine the effect of aspirin on mortality and then cardiovascular endpoints. As a consequence of the results of that study we have been asked to decide whether the Professional Labeling for aspirin should be modified to include a new claim: prevention of a primary myocardial infarction.

1) The PHS study, on the basis of recommendations from their Data Monitoring Board, was terminated early because of:

a. A substantial (about 50%) and highly statistically significant reduction in the risk of total (fatal and non-fatal) myocardial infarction in the aspirin group.

b. The inability of the trial, because of the unanticipated low mortality, to detect an effect on total cardiovascular mortality (the stated primary endpoint of the trial) until the year 2000 or later.

c. The common use of aspirin after any non-fatal vascular event (secondary prevention, is already in professional labeling), which would have made overall interpretation of results difficult.

The primary endpoint declared in all written material was total cardiovascular mortality and stopping rules based upon that endpoint were prespecified. Other possible reasons to stop the trial were not prespecified and the total incidence of myocardial infarction was only one of a number of secondary endpoints. The Data Monitoring Board, was aware of this, but for the above reasons, and noting the extreme statistical significance opted for termination.

Does this alteration in reasons for terminating the trial alter the inference that can be drawn from the results?

2) Although the PHS was a primary prevention trial, Dr. Triantas found some patients who had evidence of myocardial infarction (8% of the 512 patients who had a non-fatal acute myocardial infarction) and an additional 7% of the 512 patients had PTCAs or CABG prior to study entry.

To what extent do you think this finding alters the inference that can be drawn from the results?

3) What conclusion do you draw from the PHS trial with respect to:

a. The effect of aspirin compared to placebo on the incidence of fatal and non-fatal myocardial infarction?

b. The effect of aspirin compared to placebo on the incidence of first (fatal plus non-fatal) myocardial infarction?

c. The effect of aspirin compared to placebo on the incidence of total cardiovascular mortality?

d. The effect of aspirin compared to placebo on the incidence of fatal strokes?

e. The effect of aspirin compared to placebo on the incidence of hemorrhagic stroke?

4) Do you think the results of the British Doctors Trial (no significant difference or favorable trend) alter the inferences that should be drawn from the PHS?

5) Do you recommend that the results of the PHS trial be incorporated into the Professional Labeling of aspirin?

6) If so, should the addition be:

a. Added as in indication for primary myocardial infarction with distinction being made between fatal and non-fatal myocardial infarction; leaving the current indication as is stands?

b. Modifying the existing indication to read any myocardial infarction (primary or secondary)?

c. Qualifying any claim with respect to primary myocardial infarction with a neutral effect on total cardiovascular mortality?

d. If a., b. or c. are not satisfactory choices, how would you recommend the information derived from the PHS study be incorporated into labeling?

7) The dose studied in the PHS was 325 mg every other day. This dosing regimen is different from the current labeling recommendation for secondary prevention, 325 mg daily. If you recommend incorporation of the PHS study into labeling:

a. Should there be a single dosing recommendation? If so, which or

b. Should secondary prevention claims continue to recommend 325 mg daily while primary prevention claims recommend 325 q2d?

8) Should there be qualifications with respect to the use of aspirin such as:

a. Not for use in hypertensive patients?

b. Not for use in patients with low risk of myocardial infarction?

c. Other?

9) How should the risks be incorporated into labeling?

FOOD AND DRUG ADMINISTRATION
Center for Drug Evaluation and Research
Cardiovascular and Renal Drugs Advisory Committee
59th Meeting, October 5-6, 1989
National Institutes of Health
Building 10, Jack Masur Auditorium
9000 Rockville Pike
Bethesda, Maryland

AGENDA

Thursday, October 5, 1989

OPEN SESSION

9:00 a.m. Open Public Hearing: One hour allocated: The meeting will proceed at the conclusion of the public presentation

Anti-arrhythmic guidelines:

Introduction - Craig Pratt, M.D.
Chair

Statistical problems in estimating events of low frequency - Frank Harrell, M.D.
Committee Biostatistician

Review of mortality results with anti-arrhythmic drugs - Curt Furberg, M.D.
Bowman Grey, School of Medicine

Design of cardiac arrhythmia suppression trial (CAST) - Larry Friedman, M.D.
NHLBI

CAST classification of sudden death - Leon Greene, M.D.
CAST Cardiologist

CAST results - Alfred Hallstrom, Ph.D.
Director CAST Center

CAST sub-group analysis - Salim Yusuf, M.D., D.Phil
NHLBI

Utility of holters and electrophysiologic testing in drug testing - Jeremy Ruskin, M.D.
Cardiovascular & Renal Drugs Advisory Committee

Subgroups of patients with ventricular arrhythmias - Milton Packer, M.D.
Cardiovascular & Renal Drugs Advisory Committee

Subgroups of patients with supraventricular arrhythmias
- Edward Pritchett, M.D.
Cardiovascular & Renal Drugs Advisory Committee

12:30 p.m. Lunch

1:30 p.m. Comments from Invited Guests

FDA Invited Guests: Phillip J. Podrid, M.D.
University Hospital, Boston, MA

Albert M. Waldo, M.D.
Case Western Reserve, Clevelano, OH

Douglas P. Zipes, M.D.
Indiana University School of
Medicine, IN

Peter J. Schwartz, M.D.
Fielologia Clinica
Milano, Italy

FDA Invited Consultant: Peter R. Kowey, M.D.
Medical College of Pennsylvania
Philadelphia, PA

Committee discussion and recommendations

5:30 p.m. ADJOURN

Friday, October 6, 1989

OPEN SESSION

9:00 a.m. - Open committee discussion on NDA 18-830 Tambocor (flecainide) for supraventricular tachycardia (SVT), sponsored by Riker Laboratories

Sponsors presentation: Agenda attached

FDA Medical Reviewer: Sughok K. Chung, M.D.

FDA Statistical Reviewer: Nancy Smith, Ph.D.

Committee Reviewer: Jeremy Ruskin, M.D.

Committee discussion and recommendations

12:30 p.m. Lunch

1:30 p.m. The Physicians' Health Study: Aspirin for the prevention of myocardial infarction

Dr. Henneken's agenda attached

FDA Medical Reviewer: Eugenia T. Triantas, M.D.

FDA Statistical Reviewer: Pie Hua Ng, Ph.D.
James Hung, Ph.D.

Committee Reviewer: Craig Brater, M.D.

Committee discussion and recommendations

FDA Advisory Committee Meeting
on Aspirin for Primary Prevention of CVD

October 6, 1989

Rockville, MD

Agenda

Aspirin in the Primary Prevention of CVD:
The Physicians' Health Study

Background and Rationale (10 minutes)	Charles Hennekens, Principal Investigator
Subjects and Methods of Procedure (5 minutes)	Julie Buring, Co-Principal Investigator
Method of Ascertainment of CVD Endpoints Nonfatal Endpoints (5 minutes) Fatal Endpoints (5 minutes)	Samuel Goldhaber, Cardiologist James Taylor, Chairman, Endpoints Committee
Methods of Analysis (5 minutes)	Bernard Rosner, Statistician
Results (10 minutes)	Julie Buring, Co-Principal Investigator
Interpretation (10 minutes)	Charles Hennekens, Principal Investigator

Also present:

Fran Stubblefield, Senior Systems Analyst

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QUESTIONS

Cardiovascular and Renal Drugs Advisory Committee

October 6, 1989

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